

Gopakumar Nair Associates

Patent and Trademark Attorneys
IPR CONSULTANTS & ADVISORS



Address : "Shivmangal" 3rd Floor, Near Big Bazaar,
Akurli Road, Kandivali(East), Mumbai-400 101,
Maharashtra, India.
E-mail : 1) gopnair@gnaipr.net 2) gnaipr@vsnl.net
Website : www.gnaipr.com
Tel. : 91-22-40895454 / 28872058 / 28850805
Fax : 91-22-28462455
Mobile : 093211 52272 (Dr. Nair); 09869011185 (Mr. Sajeer)
09892583300 (Dr. Aruna)

- Patents
- Trademarks
- Designs
- Copyrights
- Contractual Agreements

GNA/AF/059/17-18

10th October, 2017

To,
The Patent Office,
Government of India,
Intellectual Property Rights Building,
G.S.T. Road, Guindy,
Chennai – 600 032.
Phone: (91)(44) 2250 2081-84

Dear Sir,

Sub: Pre-grant Representation/Opposition to the Patent Application under Section 25(1) of the Patents Act, 1970 and Rule 55(1) of the Patents Rules, 2003 (amended upto 2014)

Reg: Patent Application No. 6460/CHENP/2012A published under Section 11A on 13th February, 2015.

We are filing this Pre-grant representation/Opposition under Section 25(1) of the Patents Act, 1970 read with Rule 55(1) of the Patents Rule, 2003 on Form 7A. The Written Statement and evidence (attached herewith as Annexures/Exhibits) are enclosed herewith in duplicate.

As per provision of the Patent Act, 1970, we are entitled to file this Pre-grant Opposition any-time before grant of patent. As per the status available under inPASS, the Official website of the Indian Patent Office, the Application is 'Awaiting Examination'.

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- Technology Search, Sourcing and Transfer
- Licensing
- Prior Art Search
- Infringement Analysis
- Patentability Opinion
- Pre & Post Grant Opposition
- Revocation
- IP Enforcement and Legal Services

Pune (Mrs. Srividya Ravi - Mobile: 09860010252)

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Address : "Shivmangal" 3rd Floor, Near Big Bazaar,
Akurli Road, Kandivali(East), Mumbai-400 101,
Maharashtra, India.

E-mail : 1) gopnair@gnaipr.net 2) gnaipr@vsnl.net

Website : www.gnaipr.com

Tel. : 91-22-40895454 / 28872058 / 28850805

Fax : 91-22-28462455

Mobile : 093211 52272 (Dr. Nair); 09869011185 (Mr. Sajeew)
09892583300 (Dr. Aruna)

:: 2 ::

This pre-grant opposition is being filed by us on behalf of Cancer Patients Aid Association. We request you to take this Pre-grant Opposition on record and process the same accordingly.

We further request you to provide to us a copy of the Reply Statement and evidence and further claim amendments, if any, filed by Patent Applicant. We also request you to grant us a personal hearing under Rule 55(1).

Also, please find enclosed herewith Form 26 (Power of Attorney), in original.

Kindly acknowledge receipt.

With best regards,

Dr. Gopakumar G. Nair

Regn. No: IN/PA 509

Gopakumar Nair Associates

Encl : as above

C.C: D. P. Ahuja & Co. 14/2, Palm Avenue, Calcutta 700 019, India.

P.S.: File size of the Exhibits exceeds limit. Hence, only the representation has been filed online. Accordingly, the Representation & Exhibits are being filed as hard copy at Patent Office & served on the Agent of the Patent Applicant.

FORM 7-A
THE PATENTS ACT, 1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[Rule 55]

We, Cancer Patients Aid Association, hereby give representation by way of opposition to the grant of patent in respect of application no. **6460/CHENP/2012** dated 23rd July, 2012 filed by Pfizer Inc and published on 13th February, 2015 on the grounds of

1. Section 25(1)(b),
2. Sections 25(1)(d),
3. Section 25(1)(e) and
4. Section 25(1)(f)

Our address for service in India is

Gopakumar Nair Associates
3rd floor, Shivmangal, Next to Big Bazaar,
Akurli Road, Kandivli (East), Mumbai-400101
Maharashtra, India. Phone: 91-22-40895454
E-mail address: gopanair@gnaipr.net

Dated this 10th day of October, 2017



Dr. Gopakumar G. Nair

(Reg No. IN/PA 509)

(Agent for the Opponent)

Gopakumar Nair Associates

To
The Controller of Patents,
The Patent Office, At Chennai

BEFORE THE CONTROLLER OF PATENTS AT CHENNAI

IN THE MATTER OF

Section 25(1) of The Patents Act 1970, as amended, up to The Patents (Amendment) Act, 2005

And

IN THE MATTER OF

Rule 55 of The Patents Rules, 2003, as amended upto the Patents (Amendment) Rules, 2016

And

IN THE MATTER OF

National Phase Patent Application No. **6460/CHENP/2012** filed by **PFIZER Inc.** on July 23, 2012 claiming priority from **February 12, 2010.**

..... APPLICANT

And

IN THE MATTER OF

Pre-grant representation by way of opposition filed by the **CANCER PATIENTS AID ASSOCIATION**, a registered NGO, having its registered head office at 5, Malhotra House, Opposite GPO, Mumbai – 400 001

..... OPPONENT

STATEMENT OF FACTS/ EVIDENCE

1. It is respectfully submitted on behalf of Cancer Patients Aid Association (CPAA), a charitable organization registered under the Societies Registration Act, 1860 in January 1970 and under the Bombay Public Trusts Act, 1940 in

February 1970, having its main office and place of business at Mumbai (hereinafter referred to as "Opponent") that a representation by way of opposition is being made against the grant of patent application titled: "*SALTS AND POLYMORPHS OF 8 FLUORO 2{4 (METHYLAMINO) METHYL PHENYL} 1 3 4 5 TETRAHYDRO 6H AZEPINO [5 4 3 CD] INDOL 6 ONE*", filed by the Applicant PFIZER Inc., having their office in the United States of America, 235 East 42nd Street, New York, New York 10017, USA, bearing Indian Patent Application No. 6460/CHENP/2012, filed through their agents in India.

It is submitted by the Opponent as follows:

LOCUS STANDI

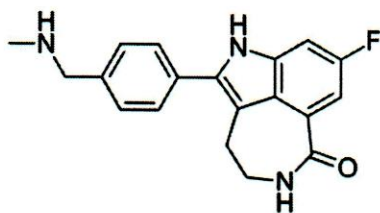
2. That Representation by way of Opposition can be made by any person, in writing under Sec. 25(1) of The Patents Act, 1970. Notwithstanding, the Opponent submits that they are interested (under Sec.2 (1)(t)) in the field of the present invention and have *locus standi* to initiate the present Pre-grant Opposition proceedings. The Opponent has real and substantial interest in the aforesaid patent application being opposed.
3. The Opponent is filing this Pre-Grant Opposition against the claims of Applicant as amended by September 2012.

JURISDICTION

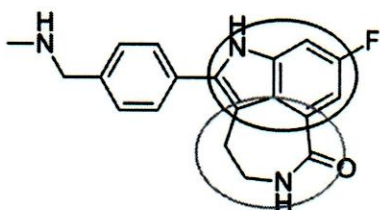
4. The patent application has been filed by Pfizer Inc. at the Patent Office in Chennai, therefore, the Patent Controller has the jurisdiction to hear this Pre-grant Opposition in Chennai. The Pre-grant Opposition is being filed on Form-7A under Section 25 (1) Of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 and Rule 55 (1) of the Patents Rules, 2003 as amended by the Patents (Amendment) Rules, 2016. Any submission made or evidence adduced with specific reference to any subsection of Sec. 25(1) may be treated as being made without prejudice to other submissions made elsewhere in this Representation by way of Opposition.
5. The Opponent submits that the grant of the impugned patent application reciting amended Claims 1 to 25 is being opposed by availing strong and valid grounds provided under Section 25(1) of the Patent Act 1970 (amended up to date by the Patents (Amendment) Act, 2005), hereinafter referred to as “the Act” and are consequently filing the present representation/ Pre-grant Opposition to the impugned patent application.

BACKGROUND

6. The present application makes claims of the camsylate and maleate salt forms of *rucaparib*. The structure of the parent compound is:



7. The core structure is a tricyclic component. It is also a fusion of an indole nucleus (marked in red - the ring on top - in the following figure) to an azepane ring (marked in blue – the ring below - in the following figure).



8. Indole was first obtained by Adolf von Baeyer in 1866 while decomposing Indigo. Indole is widely distributed in the natural environment. Indole is an aromatic heterocyclic organic compound with formula C_8H_7N . It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. The amino acid tryptophan is an indole derivative.
9. Indole is a well-known privileged scaffold occurring in numerous natural products such as alkaloids, peptides, and various synthetic compounds. Plants and fungi that contain indole alkaloids have a long history of use in traditional medicine. The oldest group of the plant alkaloids used to treat cancer are the vinca alkaloids. The vinca alkaloids were found in the 1950's by Canadian

scientists, Robert Noble and Charles Beer [Historical Review of Vinca Alkaloids, *Acta Radiologica: Diagnosis*, 8: sup291, 7-12, 1969].

10. Indole has been the parent component of a large number of compounds that occur in nature. Indoles have a great deal of attention amongst the scientific community due to its therapeutic uses. Indole and its derivatives are known to have anti-cancer, anti-inflammatory, anti-malarial, anti-microbial, anti-oxidant, antiviral, aromatase inhibition, anti-fungal, Hepatitis C virus genotype activity, hepsin inhibition, amongst many other properties.

11. The azepane moiety has been a part of many drug candidates either in the saturated form or in the unsaturated azepin form. Azepin based anti-cancer agents have been known to be effective protein kinase inhibitors, apoptosis modulators, tubulin inhibitors, Ras and Ftsase inhibitors, photo therapeutic agents, hormones modulator, histone deacetylase, and others. Since the year 2000, there have been advancements in the development of azepine based anti-cancer compounds, indicating the use of azepine for more than one and half decades.

12. Heterocyclic compounds combined and fused to form polycyclic frameworks are known to have diverse physical, chemical, and biological properties. It is therefore not surprising that heterocyclic structures have received special attention in combination synthesis and molecular scaffolds, etc. Apart from bicyclic drugs, tricyclic chemical moieties have also been a part of various

medically useful agents. Since 1971, researchers have been trying to assess the anti-cancer activity of centrally-acting tricyclic drugs [D. Linstead and D. Wilke; Biochemical Pharmacology. Vol. 20, pp. 839-846, 1971]. In these studies inhibition of cell growth by the tricyclic drugs was analyzed. Similarly, many studies to identify the anti-cancer effects of tricyclic agents such as clomipramine (dibenzoazepine derivative, thereby containing the benzene and azepine ring which are present in *rucaparib*) have been carried out [H. K. Rooprai, M. Christidou, and G. J. Pilkington; Acta Neurochir 145: 683–690; 2003].

13. Thus, considering the anti-cancer activity of individual core structures as well as the tricyclic moieties, it would be one of the most promising strategies to fuse the two cores into a tricyclic moiety as seen in *rucaparib*.

14. The salt forms, camsylate and maleate salts have been known in chemistry for a long time, and thereby the present patent application lacks novelty or inventive step and it ought to be dismissed.

PATENT APPLICANT'S MAIN CONTENTION

15. The present application is for the camsylate and maleate salt forms of *rucaparib*. The molecule *rucaparib* was patented in India on June 8, 2006, being Patent No. IN 200884, in Application No. IN/PCT/2001/00805/MUM, filed on 6.7.2001 (corresponding to Patent No. US 6495541 B1, filed on

10.1.2000) that will expire on **January 10, 2020**. The patent was assigned to Agouron Pharmaceuticals Inc.(a subsidiary of Pfizer Inc.) and Cancer Research Campaign Technology Limited.

16.The Patent Applicant, Pfizer Inc. filed the present application In India on 23.7.2012 that was published on 13.2.2015. It is the national phase entry of International PCT Application No. PCT/IB2011/0505711, bearing international publication number WO 2011/098971 A1.The PCT application was filed on 10.02.2011, claiming priority from 12.02.2010. The **priority date of the present application is 12th February 2010**. The Bibliographic page along with the amended claims and complete specification of the National Phase Application No. 6460/CHENP/2012, retrieved from the Indian Patent Office website, is hereto annexed and marked as “**Annexure 1**”.

17. It appears that the Applicant has filed the present application for salt forms of the patented drug, *rucaparib*, only to ever green the patent. The Opponent states that if a patent is granted on the present application, the patent period and monopoly for the drug *rucaparib* would extend to **10.2.2031**, that is, an extension of about **11 years** from the current expiry date of the patent in 10.1.2020! The patent ought not to be granted, as it is not patentable in India and it would extend the monopoly of the patent applicant that would be deleterious to the health and public health of the citizens in India.

18. The application when originally filed had 25 claims that were later amended on 13.9.2012. The present amended application also recites 25 claims for camsylate and maleate salts of *rucaparib*, their crystalline anhydrous salt and polymorph salt forms too.

19. Claim 1 and claim 11 are independent and the rest are dependent claims on claims 1 and 11. Claim 1 covers the camsylate salt and Claim 11 covers the maleate salt of *rucaparib*.

20. The remaining claims 2 to 10 are dependent on claim 1 and claims 12 to 21 are dependent on claim 11.

21. Claim 22 is for a pharmaceutical composition comprising of the salt of any of the claims from claim 1 to 21.

22. Claim 23 is for a method of treating mammalian disease condition mediated by poly (ADP-ribose) polymerase activity and Claim 24 is for a method of treating cancer in a mammal wherein both these claims are also for method of administering therapeutically effective amount of the pharmaceutical composition of Claim 22.

23.Claim 25 is the use of salt of any one of the claims 1 to 21 in the manufacture for a medicament for the treatment of cancer.

24.The Applicant claims to identify camsylate and maleate salts as more stable and less hygroscopic salts of *rucaparib* for formulating into a solid dosage form. However, the prior art documents and prior applications and patents of the Applicant disclose the use of the suitable salt forms, including the camsylate and maleate salts.

25.The Applicant is seeking a patent for known forms of salts that are not only obvious to a person skilled in the art, but that have already been claimed earlier. There is no novelty, no inventive step, and the application does not deserve a patent under section 3 of the Patents Act. Therefore, the present Application should be rejected *in toto*.

26.The Opponent is filing this opposition as the claims of the Applicant are not a genuine therapeutic invention, lack novelty, lack inventive step, and are obvious to a person skilled in the art.

27.The prior art annexed to the present pre-grant opposition shows clearly that the claimed compound is known prior to the priority date of the present Application and does not involve an inventive step. The claims are not patentable under Section 3(d) of the Act, as it is a salt form of a known

substance, with no enhanced efficacy. The grounds of opposition have been laid down herein below as being under section 25(1).

28. Poly ADP Ribose Polymerase (PARP) inhibitors are a group of pharmacological inhibitors of the enzyme PARP. They are developed for the treatment of cancer. *Rucaparib* is a PARP inhibitor used as an anti-cancer agent. It is a first class drug targeting the DNA repair enzyme PARP-1. It is used for treatment of ovarian cancer, BRCA 1 & 2 mutation breast cancer, and pancreatic cancer. In India breast cancer, cancer of the cervix, followed by ovarian cancer are the leading causes of cancer in women. Pancreatic cancer, though low in incidence, has an exceptionally high rate of mortality worldwide, and in India over the years there is an increased incidence of such cancers.

29. The Opponent further states that the right to health as guaranteed under Article 21 of the Constitution of India is paramount, and medicines required for the treatment of cancer, including medicines for breast cancer, ovarian cancer, pancreatic cancer, and other types of cancer ought to be made available at affordable prices to the people in the country. Wrongfully granting a patent to the Applicant would breach the right to life of many patients with cancer who ought to be able to obtain medicines at affordable prices. The price of *rucaparib* in the USA is very high (about US\$6800 to \$8200 per month dosage). This price is way beyond the reach of people in India. It is a monopolistic price, and if the patent is wrongly granted, it would prevent

competition that could have otherwise helped to bring down the prices of the drugs, allowing people to get the drugs at an affordable price.

PRE-GRANT OPPOSITION ON THE FOLLOWING GROUNDS:-

30. *Section 25(1): Opposition to the patent where the application has been published but not granted.* The following grounds and evidence sets out the basis of the opposition to the present Application. It is submitted that the impugned patent application claiming invention is not an invention within the meaning of Section 2(1)(j) of the Patents Act, is not new, does not involve an inventive step as defined under section 2(1)(ja) and is not a new invention as defined under section 2(1)(l) as it has been anticipated by prior publication. Under section 3(d) of the Act, derivatives, salts, esters, polymorphs, crystalline forms, etc. of known substances are not patentable. The present application is for a salt of a known substance and therefore ought not to be patented.
31. The Opponent is filing this pre-grant opposition on the grounds stated in Section 25(1) of the Patents Act. The primary grounds of opposition are under (i) Section 25(1)(b): that the invention so far claimed has been published before the priority date of the claim; (ii) Section 25(1)(d): as the invention so far claimed has been publicly known and used in India before the priority date in the present application; (iii) Section 25(1)(e): as the invention so claimed is obvious and clearly does not involve an inventive

step; and (iv) Section 25(1)(f): as the invention so claimed is not patentable in India under the Act.

32. The primary grounds of opposition under section 25(1) that the invention so far claimed has been published and claimed before the priority date of the claims in the following list of documents filed herewith:

- (a) **Exhibit A: Patent No. US6495541 B1**, titled “Tricyclic inhibitors of poly (ADP-ribose) polymerase”, (corresponding to the Indian patent application IN/PCT/2001/00805/MUM, patent No. **IN200884 (Exhibit A(1))**, filed by Agouron Pharmaceuticals Inc. and Cancer Research Campaign Technology Ltd. in India on 6.7.2001 bearing priority date of 11.1.1999).
- (b) **Exhibit B: WO 2004/087713 A1**, titled “Salts of tricyclic inhibitors of poly (ADP-ribose) polymerases”, filed by Pfizer Inc. on 19.3.2004.
- (c) **Exhibit C: US 2006/0074073 A1** titled “Therapeutic combinations comprising poly (ADP-ribose) polymerases inhibitors”, filed by Agouron Pharmaceuticals Inc; Cancer Research Technology Ltd., filed on 20.9.2005, that has an equivalent Indian Application being IN/1514/DELNP/2007 (the Indian application has been abandoned under section 21(1)).
- (d) **Exhibit D: Review Article: Berge, S, Bighley, L and Monkhouse, D**, “Pharmaceutical salts”, Journal of Pharmaceutical Sciences, January 1977, Volume 66 Number 1.

- (e) **Exhibit E: US 6936625 B2**, titled “Amlodipine camsylate and method for preparing thereof”, filed by Hanmi Pharma Co. Ltd. on 28.3.2002.
- (f) **Exhibit F: US 4489011 A**, titled “Hypoglycemic N-(2-substituted-3-dialkylamino – 2- propenylidene) – N- alkylalk- anaminium camsylate salts”, filed by Merrell Dow Pharmaceuticals on 16.5.1983.
- (g) **Exhibit G:US 4879303 A**, titled “Pharmaceutically acceptable salts”, filed by Pfizer Inc. on 13.10.1988.

33. The Opponent states that none of the claims of the Applicant should be deemed accepted, unless specifically admitted/ accepted herein. The Opponent opposed all the claims of the Applicant and states that the patent application should be dismissed *in toto*.
34. The grounds of opposition of claims 1 to 25 are primarily based on provisions of Section 25(1) read with Sections 2, 3, 10 and of the Act as specified hereto.
35. The Opponent states that the Applicant has made claims for the salt forms of known structures that have been known prior to the priority date of the present Application, and are also obvious to a person skilled in the art. Thus, no claim for a patent can be made by the Applicant.

GROUND OF OPPOSITION

36. The Opponent now deals with following relevant grounds of pre-grant opposition under Section 25(1) substantiated with facts disclosed in the prior art documents.

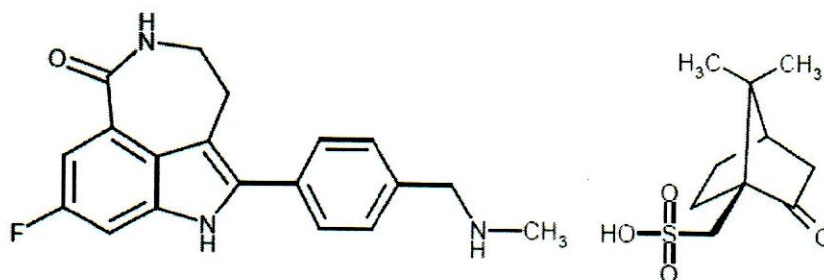
A. Section 25(1)(b): Lack of Novelty/Prior publication

- (i) The Opponent submits that the impugned patent application is ineligible for grant of patent under Section 25(1)(b) of the Patents Act, 1970.
- (ii) Claims 1-21 and 22-25 (as amended on 13.9.2012) of the present application are not novel in view of **Exhibit A**, Patent No. US 6495541 B1 or the Indian equivalent patent IN 200884 (**Exhibit A(1)**), granted for “tricyclic inhibitors of poly(ADP-ribose) polymerases”, having priority from 11.1.1999, which are useful as therapeutics in treatment of cancers and the amelioration of other conditions. The documents at **Exhibit A and Exhibit A(1)** disclose the pharmaceutically acceptable salts, prodrugs, active metabolites and solvates of the compounds. It is stated in the document that “pharmaceutically acceptable salts” are those intended to mean a salt that retains the biological effectiveness of the free acid and base form of the specified compound and that is pharmaceutically suitable. Examples of pharmaceutically acceptable salts at **Exhibit A and Exhibit A(1)** include maleates. The document further states that **in case of compounds, salts that are solids, it is understood by those skilled in the art that the compounds, salts and**

solvates may exists in different crystalline or polymorph forms [See Exhibit A columns 9 - 11].

- (iii) The salt forms of *rucaparib* have been claimed in the document at **Exhibit B**, WO2004/087713 A1, in which salts of 8-fluoro-2-(4-methylaminomethyl-phenyl)- 1, 3, 4, 5-tetrahydro-azepino [5, 4, 3- cd] indol- 6-one have been claimed. The document specifies the use of the compound for treatment of cancers and the amelioration of diseases. As cancer therapeutics, the compounds of the invention maybe used in combination with DNA damaging cytotoxic agents too. Though the document at **Exhibit B** does not specify the camsylate and maleate salt forms, it broadly claims the pharmaceutically acceptable salt form of the compound, and later specifically also claims the phosphate salt form [See **Exhibit B** page 3-6].
- (iv) The claims 1-25 in the present application are not novel, and have been prior claimed and published in the document at “**Exhibit C**”, US 2006 0074073 (Indian equivalent IN1514/DELNP/2007) that discloses and claims the dosage form of *Rucaparib* along with pharmaceutically acceptable salts, solvates and its combination with other anti-cancer agents. It specifically states that the compound is therapeutically effective for many types of cancers, including pancreatic cancer, ovarian cancer, etc. [See **Exhibit C** page 3 paras 0020-0027].

- (v) The document at **Exhibit C** also includes the camsylate and maleate salt forms of the said form of *rucaparib* [See **Exhibit C** pages 2- 4, paras 0009-0017, and 0043]. The structure of the compound at **Exhibit C** is exactly the same as that claimed in the present application, and envisages the salt forms too:-



- (vi) Thus, the present application is not novel, the compound and its salts forms have been known and envisaged in documents prior to the priority date of the application herein, and the impugned application ought to be rejected under Section 25(1)(b).

B. Section 25(1)(d): Prior public knowledge and prior use in India

- (i) The prior art documents at **Exhibits A to G**, the invention so far claimed in the present application for the salt forms of *rucaparib* and its use in the treatment as an anti-cancer agent has been known and used in India prior to the priority date of the impugned application.
- (ii) The pharmaceutically acceptable salt form of the compound and its use

thereof has been known. The camsylate and maleate salt forms have been known to have better stability, solubility, non-hygroscopicity and suitable for solid forms of the compound. The use of camsylate and maleate salts for *rucaparib* is not inventive, nor is it novel, it is in fact obvious and their use and properties as pharmaceutically acceptable salts have been known for decades. Thus the impugned application ought to be rejected on the ground of Section 25(1)(d) of the Patents Act.

C. Section 25(1)(e) : Obviousness and Lack of inventive step

- (i) The Opponent submits that the alleged invention clearly lacks an inventive step, and is obvious to a person of ordinary skills in the art. As such the Indian Patent Application 6460/CHENP/2012 is ineligible for grant of patent under section 25(1)(e) of the Patents Act.
- (ii) The Applicant states that the prior art used the phosphate salt form which was suitable for the intravenous dosage, but unsuitable for the solid dosage form. The applicant states that they have found the camsylate and maleate salt of *rucaparib* to be stable and not susceptible to hydration compared to other salt forms. However, these properties of the camsylate and maleate salt forms are known and use of them in solid dosage forms is not inventive.

- (iii) The Opponent submits that the document at “**Exhibit C**” discloses a list of salts used as the *rucaparib* salt forms, including the camsylate and maleate forms. **Exhibit A** also specifically discloses the maleate salt form of *rucaparib*.
- (iv) The pharmaceutical salts have been known since decades, and there is no novelty, no inventive step, and the uses of the salt forms are obvious to a person skilled in the art. Berge et al., 1977, the document annexed at “**Exhibit D**” discloses a list of 53 FDA approved commercially marketed salts used in pharmaceutical products which includes the camsylate and maleate salts. The document displays the knowledge that salt forms display physical, chemical, and thermodynamic properties to the parent compound – crystalline and hydrophobicity that affect the dissolution rate, stability, absorption, toxicity, hygroscopicity, etc. that affect bioavailability and solubility. The salt forms alter the physical, chemical, and biological characteristics of a drug without modifying the chemical structure. The Applicant of the impugned application would have been motivated to use the salts listed by the FDA and based on routine experimentation, identified the salts that would be suitably stable for *rucaparib* [See **Exhibit D** page 2, table 1].
- (v) The Applicant has made claims in the present application on the salt forms by specifying X-ray diffraction patterns, NMR spectrum, etc. It

may be noted that drug substances, salts, polymorphs, crystalline salt forms need to be thermodynamically stable or metastable form. Good knowledge of polymorphism and polymorphic stability is needed to predict long term stability of dosage forms, including crystalline and anhydrous crystalline forms. There are various techniques to study or investigate the solid state. These include x-ray, x-ray powder diffraction, thermal analysis, etc. Powder x-ray diffraction is both rapid and relatively simpler and is a known method of choice. It is unique to each polymorphic form, and are known in chemistry [See text book Herbert Lieberman, Leon Lachman and Joseph Schwartz, "Pharmaceutical Dosage Forms: Tablets" Volume 1, 1989; pages 38 – 41]. No patent can be claimed on techniques used to study the solid state of drug substances.

- (vi) Further, the Nuclear Magnetic Resonance (NMR) Spectroscopy are observational techniques used in chemistry to observe the behaviour of atomic nuclei when subjected to external magnetic field. NMR spectroscopy is particularly useful in the context of assessing the extent of ultraviolet and infrared spectra of heteroaromatic systems are in accord with their aromatic character, their properties, in determining the position of tautomeric equilibria and in testing for existence of non-insoluble intermediaries. These are known in heterocycle chemistry and no patent can be claimed on such techniques used in pharmaceutical

science. Thus, claims 3 - 10 and 13- 21 cannot be claimed nor granted in the present application, and the present patent application should be dismissed *in limine*.

- (vii) The camsylate salt used in pharmaceutical drugs has been known to be stable and its method of preparing has been known. The camsylate salt is known to form different crystal forms that have been well analysed via X-ray diffraction and NMR spectrum analysis. This has been revealed in the document annexed at **"Exhibit E"**, US 6936625 B2 titled "Amlodipine camsylate and method of preparing thereof". Camsylate salt forms have been used for treating various diseases, including cardiovascular diseases. Thus, there is no inventive step, and the properties of camsylate salts make it an obvious and preferred candidate for use as pharmaceutical salts for better stability, etc. [See **Exhibit E** columns 1, 2, 7 and table 4].
- (viii) The Opponent also submits that camsylate and maleate salts have been used in pharmaceutical science for decades for their known stability, better physicochemical properties and hygroscopicity. The document at **"Exhibit F"**, US 4489011 A, relates to certain oral "hypoglycaemic N-(2-substituted-3-dialkylamino - 2- propenylidene) - N- alkylalk-anaminium camsylate salts". The camsylate salts have better physiochemical properties. The document at **Exhibit F** shows that

camsylate salts have desirable solubility, high stability, non-hygroscopicity, and superior palatability when compared with other corresponding alkanaminium cations [See **Exhibit F** end of Column 1].

- (ix) Camsylate salts have been found to be better than conventional salts and are neither hygroscopic nor explosive, rendering them suitable for the preparation of conventional solid dosage forms with acceptably long shelf life. It also is physiologically inert and thus introduces no unwanted side effects during long term administration [See **Exhibit F** Column 2].
- (x) The document at **Exhibit F** displays the better properties of camsylate salt and makes it the obvious choice of a person with ordinary skills in the art.
- (xi) Similarly, maleate salts also have been known for their properties to be the obvious choice for use in pharmaceutical drugs. The document at "**Exhibit G**" is US 4879303 "Pharmaceutically acceptable salts". Though the document is for the besylate salt form, it describes the properties of stability, etc. of the maleate salt form too. It can be seen in Table 1 of the document at **Exhibit G**, that the maleate salt has good solubility, like the besylate salt, and is pretty stable too. The document also describes that "only maleate, tosylate and besylate salts do not pick

up any moisture when exposed to 75% relative humidity at 37 degrees Celsius for 24 hours [See **Exhibit G** Column 2, Table 1 and Column 3].

(xii) The document at **Exhibit G** states that in order to be suitable for this purpose, the pharmaceutically acceptable salt must satisfy the following four physiochemical criteria: i. good solubility; ii. Good stability; iii. Non-hydroscopicity; and iv. Processability for tablet formulations, etc. [See **Exhibit G** Column 2].

(xiii) Thus, the document at **Exhibit G** makes maleate salt also the obvious choice for *rucaparib*.

(xiv) For all the above reasons, the present patent application ought to be dismissed, as there is no novelty, no inventive step and is obvious to a person with ordinary skills in the art.

D. Section 25(1)(f): Not an invention within the meaning of the Patents Act.

(i) It has been shown by the prior art documents annexed in the present Pre-grant Opposition that the complete specification and the amended claims do not constitute an invention. The alleged invention so far claimed is neither a new product nor a new process nor does it involve an inventive step as there is no technical advance as compared to existing knowledge

and the alleged invention is obvious to a person skilled in the art. In fact, the alleged invention is a salt form of a known substance or compound and cannot be patented in India.

(ii) The claims of the present Application also do not meet the test prescribed under Sections 2(1)(j) and 2(1)(ja) of the Act and hence the application ought to be dismissed *in limine*.

(iii) The Opponent strongly submits that the alleged invention falls within the ambit of **Section 3(d)** and hence is not patentable. The definition of Section 3(d) read alongwith explanation is relevant and validly applicable for the alleged subject matter:

Sec. 3(d) of the Act reads as “*the mere discovery of a new form of a known substance* which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the *mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant*” is **not patentable** under the Act.

Explanation:- For the purpose of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers mixtures of isomers, complexes, combinations and other derivatives of known

substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.”

- (iv) It is an established position of the law that if a discovery is made from a known compounds, a duty is cast upon the patent applicant to show that the discovery had resulted in the enhancement of a known efficacy of that substance [See *Novartis AG v. Union of India and others*, (2007), 4 MLJ 1153, page 15]. The Hon’ble Intellectual Property Appellate Board has also held in *Novartis AG v. Union of India and Others*, IPAB, 26.06.2009, at pages 178 and 179, that “efficacy” in Sec. 3(d) means therapeutic efficacy.
- (v) Salts, polymorphs, etc. of known substances are considered to be the same substance and are not patentable under Section 3(d) of the Patents Act. The impugned application is for the salt forms of *rucaparib* and is hit by Section 3(d) of the Patents Act, and the impugned application should be rejected *in toto*.
- (vi) The impugned application does not speak of the efficacy of *rucaparib*’s salt forms or enhanced properties, if any. The application only focuses on improvement of certain physiochemical parameters by using the maleate and camsylate salt forms for they hygroscopic properties in a solid form over the prior art of the phosphate salt of *rucaparib*.

However, as seen in the prior art annexed to this Opposition, it is clear that the properties of maleate and camsylate salt forms have been known and their use in *rucaparib* is not patentable as it is a mere discovery of a new form of a known substance, namely, salt and polymorph forms of *rucaparib*, with known properties and processes and no new reactants, making it to be the one and the same substance, that is, *rucaparib*.

- (vii) Further, some of the claims in the present application for techniques to analyse the solid forms of drug substances are not only frivolous but are known scientific principles and are hit by Section 3(a) and 3(c) of the Patents Act and cannot be patented.
- (viii) The prior art documents at **Exhibit A to G** not only describe the broad acceptable pharmaceutical salt forms of *rucaparib* but also describe the maleate and camsylate salt forms and show clearly why they would be the obvious choice for the pharmaceutical product.
- (ix) The claims in the impugned application at claim 23 and 24 for the method of treating the disease condition and method of treating cancer fall within the meaning of inventions not patentable under Section 3(i). Hence, not patentable.
- (x) In view of the above, the claims from claim 1 to 22 and 25 of the

impugned application ought to be rejected under section 25(1)(f) read with section 3(d) of the Patents Act, being the salt form of a known substance lacking enhanced therapeutic efficacy. Claims 23 and 24 of the impugned application ought to be rejected under section 25(1)(f) read with section 3(i) of the Patents Act, being methods of treatment, administration of the pharmaceutical composition of salts of *rucaparib* which are not patentable. Thus the impugned application ought to be rejected *in toto*.

37. It is submitted by the Opponent that all the above-mentioned prior art documents annexed to the present Pre-grant Opposition destroy the novelty of the alleged invention so claimed by the Applicant. The information in the prior art documents disclose the essential elements of the alleged invention. Novelty is destroyed when the essential elements have been disclosed, even if the details of executing the invention, or clear description of its properties or method of making it were not disclosed.
38. In *Enercon (India) Limited v. Aloys Wobben* ORA/6/2009/PT/CH, ORDER (No. 18 of 2013) the Intellectual Property Appellate Board of India noted that novelty may be denied on the basis of 'inherent anticipation'. It stated: "*the prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating prior art..... it is not necessary that inherent*

anticipation requires that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. But it is necessary that the result is a necessary consequence of what was deliberately intended in the invention."

Thus, the novelty in the present application is destroyed by all prior art documents cited herein.

39. It is further submitted that the inventive step claims in the present application are destroyed as what is claimed is obvious to a person skilled in the art, i.e. there is reasonable expectation of success embedded in the prior art which motivates a skilled person to arrive at the alleged claimed invention. Obviousness cannot be avoided by showing some degree of unpredictability in the art, so long as there was a reasonable probability of success through disclosures provided in the prior art documents. Obviousness does not require absolute predictability of success. All that is required is reasonable expectation of success in the matter of pharmaceutical inventions. All the prior art documents annexed to this Opposition provide a reasonable predictability of success and the claimed compound is obvious to a person skilled in the art. Additionally, the claimed compounds do not involve a technical advance compared to existing knowledge.
40. The Opponent states that grant of patents to the Applicant in other jurisdictions cannot tantamount to a grant of a patent in India. The Indian law is different from the laws in other jurisdictions and care has been taken by the law makers

not to allow patents for pharmaceutical products that are not genuinely inventive or that are known earlier, or obvious to a person skilled in the art. The law specifically prohibits grant of patents for salts, polymorphs, etc. of known substances and also prevents abuse of the patent process by laying down grounds for opposition that prevent undeserving patents from being granted.

41. The Opponent states that the present Application No. 6460/CHENP/2012 falls within the category of non-patentable inventions as described in Section 3(d) and 3(i) of the Patents act, and also does not meet the definition of “invention” and inventive step as set out in Section 2(1)(j) and 2(1)(ja) of the Act. The present Application ought to be rejected *in toto* under Section 25(1) read with clauses (j) and (ja) of section 2(1) and clause (d) of Section 3 of the Act.

42. **Prayers**

Having established non-patentability of the alleged invention and having adduced supporting evidence for each of the above grounds of Opposition, Opponent prays for the following reliefs:

- a. That the Applicant’s Patent Application No. 6460/CHENP/2012 having filed, with original claims as well as amended claims, be rejected *in toto* and the grant of Patent to the Applicant be refused.
- b. That the Opponent be granted leave to file further arguments and evidence against the impugned application.
- c. That copy of the reply of the Applicants and evidence, if any, be forwarded to the Opponent along with amendment to claims, if any;

- d. That the Opponent be granted leave to file response/rejoinder to the reply and the evidence of the Applicants.
- e. That the Opponent should be given an opportunity to oppose the amended claims, if any.
- f. That the Opponent be granted hearing in this case.
- g. That the Opponent be granted leave to refer to and rely upon full text of the documents referred to in this opposition.
- h. Such other and further relief/s be granted to the Opponent, as the Ld. Controller may deem fit in the facts and circumstances of this case.
- i. That the Opponent be awarded costs.

All communications relating to these proceedings may be sent to the following address in India:-

Dr. GOPAKUMAR G. NAIR
Gopakumar Nair Associates
3rd floor, Shivmangal, Next to Big Bazaar
Akurli Road, Kandivli (East), Mumbai-400101
Maharashtra, India. Phone: 91-22-40895454
E-mail address: gopanair@gnaipr.net

Dated this 10th day of October, 2017



Dr. GOPAKUMAR G. NAIR
Regn. No: IN/PA 509
(Agent for the Opponent)
Gopakumar Nair Associates

To,
The Controller of Patents
The Patent Office, Chennai

FORM 7-A
THE PATENTS ACT, 1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[Rule 55]

We, Cancer Patients Aid Association, hereby give representation by way of opposition to the grant of patent in respect of application no. **6460/CHENP/2012** dated 23rd July, 2012 filed by Pfizer Inc and published on 13th February, 2015 on the grounds of

1. Section 25(1)(b),
2. Sections 25(1)(d),
3. Section 25(1)(e) and
4. Section 25(1)(f)

Our address for service in India is

Gopakumar Nair Associates
3rd floor, Shivmangal, Next to Big Bazaar,
Akurli Road, Kandivli (East), Mumbai-400101
Maharashtra, India. Phone: 91-22-40895454
E-mail address: gopanair@gnaipr.net

Dated this 10th day of October, 2017



Dr. Gopakumar G. Nair

(Reg No. IN/PA 509)

(Agent for the Opponent)

Gopakumar Nair Associates

To
The Controller of Patents,
The Patent Office, At Chennai

BEFORE THE CONTROLLER OF PATENTS AT CHENNAI

IN THE MATTER OF

Section 25(1) of The Patents Act 1970, as amended, up to The Patents (Amendment) Act, 2005

And

IN THE MATTER OF

Rule 55 of The Patents Rules, 2003, as amended upto the Patents (Amendment) Rules, 2016

And

IN THE MATTER OF

National Phase Patent Application No. **6460/CHENP/2012** filed by **PFIZER Inc.** on July 23, 2012 claiming priority from **February 12, 2010.**

..... APPLICANT

And

IN THE MATTER OF

Pre-grant representation by way of opposition filed by the **CANCER PATIENTS AID ASSOCIATION**, a registered NGO, having its registered head office at 5, Malhotra House, Opposite GPO, Mumbai – 400 001

..... OPPONENT

STATEMENT OF FACTS/ EVIDENCE

1. It is respectfully submitted on behalf of Cancer Patients Aid Association (CPAA), a charitable organization registered under the Societies Registration Act, 1860 in January 1970 and under the Bombay Public Trusts Act, 1940 in

February 1970, having its main office and place of business at Mumbai (hereinafter referred to as "Opponent") that a representation by way of opposition is being made against the grant of patent application titled: "*SALTS AND POLYMORPHS OF 8 FLUORO 2{4 (METHYLAMINO) METHYL PHENYL} 1 3 4 5 TETRAHYDRO 6H AZEPINO [5 4 3 CD] INDOL 6 ONE*", filed by the Applicant PFIZER Inc., having their office in the United States of America, 235 East 42nd Street, New York, New York 10017, USA, bearing Indian Patent Application No. 6460/CHENP/2012, filed through their agents in India.

It is submitted by the Opponent as follows:

LOCUS STANDI

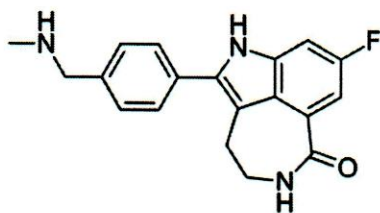
2. That Representation by way of Opposition can be made by any person, in writing under Sec. 25(1) of The Patents Act, 1970. Notwithstanding, the Opponent submits that they are interested (under Sec.2 (1)(t)) in the field of the present invention and have *locus standi* to initiate the present Pre-grant Opposition proceedings. The Opponent has real and substantial interest in the aforesaid patent application being opposed.
3. The Opponent is filing this Pre-Grant Opposition against the claims of Applicant as amended by September 2012.

JURISDICTION

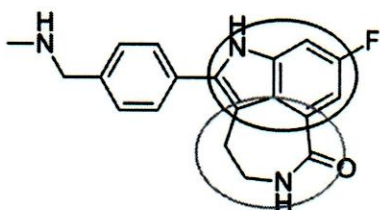
4. The patent application has been filed by Pfizer Inc. at the Patent Office in Chennai, therefore, the Patent Controller has the jurisdiction to hear this Pre-grant Opposition in Chennai. The Pre-grant Opposition is being filed on Form-7A under Section 25 (1) Of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 and Rule 55 (1) of the Patents Rules, 2003 as amended by the Patents (Amendment) Rules, 2016. Any submission made or evidence adduced with specific reference to any subsection of Sec. 25(1) may be treated as being made without prejudice to other submissions made elsewhere in this Representation by way of Opposition.
5. The Opponent submits that the grant of the impugned patent application reciting amended Claims 1 to 25 is being opposed by availing strong and valid grounds provided under Section 25(1) of the Patent Act 1970 (amended up to date by the Patents (Amendment) Act, 2005), hereinafter referred to as “the Act” and are consequently filing the present representation/ Pre-grant Opposition to the impugned patent application.

BACKGROUND

6. The present application makes claims of the camsylate and maleate salt forms of *rucaparib*. The structure of the parent compound is:



7. The core structure is a tricyclic component. It is also a fusion of an indole nucleus (marked in red - the ring on top - in the following figure) to an azepane ring (marked in blue – the ring below - in the following figure).



8. Indole was first obtained by Adolf von Baeyer in 1866 while decomposing Indigo. Indole is widely distributed in the natural environment. Indole is an aromatic heterocyclic organic compound with formula C_8H_7N . It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. The amino acid tryptophan is an indole derivative.
9. Indole is a well-known privileged scaffold occurring in numerous natural products such as alkaloids, peptides, and various synthetic compounds. Plants and fungi that contain indole alkaloids have a long history of use in traditional medicine. The oldest group of the plant alkaloids used to treat cancer are the vinca alkaloids. The vinca alkaloids were found in the 1950's by Canadian

scientists, Robert Noble and Charles Beer [Historical Review of Vinca Alkaloids, *Acta Radiologica: Diagnosis*, 8: sup291, 7-12, 1969].

10. Indole has been the parent component of a large number of compounds that occur in nature. Indoles have a great deal of attention amongst the scientific community due to its therapeutic uses. Indole and its derivatives are known to have anti-cancer, anti-inflammatory, anti-malarial, anti-microbial, anti-oxidant, antiviral, aromatase inhibition, anti-fungal, Hepatitis C virus genotype activity, hepsin inhibition, amongst many other properties.

11. The azepane moiety has been a part of many drug candidates either in the saturated form or in the unsaturated azepin form. Azepin based anti-cancer agents have been known to be effective protein kinase inhibitors, apoptosis modulators, tubulin inhibitors, Ras and Ftsase inhibitors, photo therapeutic agents, hormones modulator, histone deacetylase, and others. Since the year 2000, there have been advancements in the development of azepine based anti-cancer compounds, indicating the use of azepine for more than one and half decades.

12. Heterocyclic compounds combined and fused to form polycyclic frameworks are known to have diverse physical, chemical, and biological properties. It is therefore not surprising that heterocyclic structures have received special attention in combination synthesis and molecular scaffolds, etc. Apart from bicyclic drugs, tricyclic chemical moieties have also been a part of various

medically useful agents. Since 1971, researchers have been trying to assess the anti-cancer activity of centrally-acting tricyclic drugs [D. Linstead and D. Wilke; Biochemical Pharmacology. Vol. 20, pp. 839-846, 1971]. In these studies inhibition of cell growth by the tricyclic drugs was analyzed. Similarly, many studies to identify the anti-cancer effects of tricyclic agents such as clomipramine (dibenzoazepine derivative, thereby containing the benzene and azepine ring which are present in *rucaparib*) have been carried out [H. K. Rooprai, M. Christidou, and G. J. Pilkington; Acta Neurochir 145: 683–690; 2003].

13. Thus, considering the anti-cancer activity of individual core structures as well as the tricyclic moieties, it would be one of the most promising strategies to fuse the two cores into a tricyclic moiety as seen in *rucaparib*.

14. The salt forms, camsylate and maleate salts have been known in chemistry for a long time, and thereby the present patent application lacks novelty or inventive step and it ought to be dismissed.

PATENT APPLICANT'S MAIN CONTENTION

15. The present application is for the camsylate and maleate salt forms of *rucaparib*. The molecule *rucaparib* was patented in India on June 8, 2006, being Patent No. IN 200884, in Application No. IN/PCT/2001/00805/MUM, filed on 6.7.2001 (corresponding to Patent No. US 6495541 B1, filed on

10.1.2000) that will expire on **January 10, 2020**. The patent was assigned to Agouron Pharmaceuticals Inc.(a subsidiary of Pfizer Inc.) and Cancer Research Campaign Technology Limited.

16.The Patent Applicant, Pfizer Inc. filed the present application In India on 23.7.2012 that was published on 13.2.2015. It is the national phase entry of International PCT Application No. PCT/IB2011/0505711, bearing international publication number WO 2011/098971 A1.The PCT application was filed on 10.02.2011, claiming priority from 12.02.2010. The **priority date of the present application is 12th February 2010**. The Bibliographic page along with the amended claims and complete specification of the National Phase Application No. 6460/CHENP/2012, retrieved from the Indian Patent Office website, is hereto annexed and marked as “**Annexure 1**”.

17. It appears that the Applicant has filed the present application for salt forms of the patented drug, *rucaparib*, only to ever green the patent. The Opponent states that if a patent is granted on the present application, the patent period and monopoly for the drug *rucaparib* would extend to **10.2.2031**, that is, an extension of about **11 years** from the current expiry date of the patent in 10.1.2020! The patent ought not to be granted, as it is not patentable in India and it would extend the monopoly of the patent applicant that would be deleterious to the health and public health of the citizens in India.

18. The application when originally filed had 25 claims that were later amended on 13.9.2012. The present amended application also recites 25 claims for camsylate and maleate salts of *rucaparib*, their crystalline anhydrous salt and polymorph salt forms too.

19. Claim 1 and claim 11 are independent and the rest are dependent claims on claims 1 and 11. Claim 1 covers the camsylate salt and Claim 11 covers the maleate salt of *rucaparib*.

20. The remaining claims 2 to 10 are dependent on claim 1 and claims 12 to 21 are dependent on claim 11.

21. Claim 22 is for a pharmaceutical composition comprising of the salt of any of the claims from claim 1 to 21.

22. Claim 23 is for a method of treating mammalian disease condition mediated by poly (ADP-ribose) polymerase activity and Claim 24 is for a method of treating cancer in a mammal wherein both these claims are also for method of administering therapeutically effective amount of the pharmaceutical composition of Claim 22.

23.Claim 25 is the use of salt of any one of the claims 1 to 21 in the manufacture for a medicament for the treatment of cancer.

24.The Applicant claims to identify camsylate and maleate salts as more stable and less hygroscopic salts of *rucaparib* for formulating into a solid dosage form. However, the prior art documents and prior applications and patents of the Applicant disclose the use of the suitable salt forms, including the camsylate and maleate salts.

25.The Applicant is seeking a patent for known forms of salts that are not only obvious to a person skilled in the art, but that have already been claimed earlier. There is no novelty, no inventive step, and the application does not deserve a patent under section 3 of the Patents Act. Therefore, the present Application should be rejected *in toto*.

26.The Opponent is filing this opposition as the claims of the Applicant are not a genuine therapeutic invention, lack novelty, lack inventive step, and are obvious to a person skilled in the art.

27.The prior art annexed to the present pre-grant opposition shows clearly that the claimed compound is known prior to the priority date of the present Application and does not involve an inventive step. The claims are not patentable under Section 3(d) of the Act, as it is a salt form of a known

substance, with no enhanced efficacy. The grounds of opposition have been laid down herein below as being under section 25(1).

28. Poly ADP Ribose Polymerase (PARP) inhibitors are a group of pharmacological inhibitors of the enzyme PARP. They are developed for the treatment of cancer. *Rucaparib* is a PARP inhibitor used as an anti-cancer agent. It is a first class drug targeting the DNA repair enzyme PARP-1. It is used for treatment of ovarian cancer, BRCA 1 & 2 mutation breast cancer, and pancreatic cancer. In India breast cancer, cancer of the cervix, followed by ovarian cancer are the leading causes of cancer in women. Pancreatic cancer, though low in incidence, has an exceptionally high rate of mortality worldwide, and in India over the years there is an increased incidence of such cancers.

29. The Opponent further states that the right to health as guaranteed under Article 21 of the Constitution of India is paramount, and medicines required for the treatment of cancer, including medicines for breast cancer, ovarian cancer, pancreatic cancer, and other types of cancer ought to be made available at affordable prices to the people in the country. Wrongfully granting a patent to the Applicant would breach the right to life of many patients with cancer who ought to be able to obtain medicines at affordable prices. The price of *rucaparib* in the USA is very high (about US\$6800 to \$8200 per month dosage). This price is way beyond the reach of people in India. It is a monopolistic price, and if the patent is wrongly granted, it would prevent

competition that could have otherwise helped to bring down the prices of the drugs, allowing people to get the drugs at an affordable price.

PRE-GRANT OPPOSITION ON THE FOLLOWING GROUNDS:-

30. *Section 25(1): Opposition to the patent where the application has been published but not granted.* The following grounds and evidence sets out the basis of the opposition to the present Application. It is submitted that the impugned patent application claiming invention is not an invention within the meaning of Section 2(1)(j) of the Patents Act, is not new, does not involve an inventive step as defined under section 2(1)(ja) and is not a new invention as defined under section 2(1)(l) as it has been anticipated by prior publication. Under section 3(d) of the Act, derivatives, salts, esters, polymorphs, crystalline forms, etc. of known substances are not patentable. The present application is for a salt of a known substance and therefore ought not to be patented.
31. The Opponent is filing this pre-grant opposition on the grounds stated in Section 25(1) of the Patents Act. The primary grounds of opposition are under (i) Section 25(1)(b): that the invention so far claimed has been published before the priority date of the claim; (ii) Section 25(1)(d): as the invention so far claimed has been publicly known and used in India before the priority date in the present application; (iii) Section 25(1)(e): as the invention so claimed is obvious and clearly does not involve an inventive

step; and (iv) Section 25(1)(f): as the invention so claimed is not patentable in India under the Act.

32. The primary grounds of opposition under section 25(1) that the invention so far claimed has been published and claimed before the priority date of the claims in the following list of documents filed herewith:

- (a) **Exhibit A: Patent No. US6495541 B1**, titled “Tricyclic inhibitors of poly (ADP-ribose) polymerase”, (corresponding to the Indian patent application IN/PCT/2001/00805/MUM, patent No. **IN200884 (Exhibit A(1))**, filed by Agouron Pharmaceuticals Inc. and Cancer Research Campaign Technology Ltd. in India on 6.7.2001 bearing priority date of 11.1.1999).
- (b) **Exhibit B: WO 2004/087713 A1**, titled “Salts of tricyclic inhibitors of poly (ADP-ribose) polymerases”, filed by Pfizer Inc. on 19.3.2004.
- (c) **Exhibit C: US 2006/0074073 A1** titled “Therapeutic combinations comprising poly (ADP-ribose) polymerases inhibitors”, filed by Agouron Pharmaceuticals Inc; Cancer Research Technology Ltd., filed on 20.9.2005, that has an equivalent Indian Application being IN/1514/DELNP/2007 (the Indian application has been abandoned under section 21(1)).
- (d) **Exhibit D: Review Article: Berge, S, Bighley, L and Monkhouse, D**, “Pharmaceutical salts”, Journal of Pharmaceutical Sciences, January 1977, Volume 66 Number 1.

- (e) **Exhibit E: US 6936625 B2**, titled “Amlodipine camsylate and method for preparing thereof”, filed by Hanmi Pharma Co. Ltd. on 28.3.2002.
- (f) **Exhibit F: US 4489011 A**, titled “Hypoglycemic N-(2-substituted-3-dialkylamino – 2- propenylidene) – N- alkylalk- anaminium camsylate salts”, filed by Merrell Dow Pharmaceuticals on 16.5.1983.
- (g) **Exhibit G:US 4879303 A**, titled “Pharmaceutically acceptable salts”, filed by Pfizer Inc. on 13.10.1988.

33. The Opponent states that none of the claims of the Applicant should be deemed accepted, unless specifically admitted/ accepted herein. The Opponent opposed all the claims of the Applicant and states that the patent application should be dismissed *in toto*.
34. The grounds of opposition of claims 1 to 25 are primarily based on provisions of Section 25(1) read with Sections 2, 3, 10 and of the Act as specified hereto.
35. The Opponent states that the Applicant has made claims for the salt forms of known structures that have been known prior to the priority date of the present Application, and are also obvious to a person skilled in the art. Thus, no claim for a patent can be made by the Applicant.

GROUND OF OPPOSITION

36. The Opponent now deals with following relevant grounds of pre-grant opposition under Section 25(1) substantiated with facts disclosed in the prior art documents.

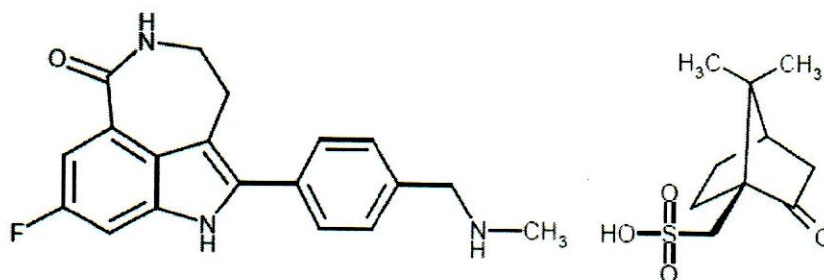
A. Section 25(1)(b): Lack of Novelty/Prior publication

- (i) The Opponent submits that the impugned patent application is ineligible for grant of patent under Section 25(1)(b) of the Patents Act, 1970.
- (ii) Claims 1-21 and 22-25 (as amended on 13.9.2012) of the present application are not novel in view of **Exhibit A**, Patent No. US 6495541 B1 or the Indian equivalent patent IN 200884 (**Exhibit A(1)**), granted for “tricyclic inhibitors of poly(ADP-ribose) polymerases”, having priority from 11.1.1999, which are useful as therapeutics in treatment of cancers and the amelioration of other conditions. The documents at **Exhibit A and Exhibit A(1)** disclose the pharmaceutically acceptable salts, prodrugs, active metabolites and solvates of the compounds. It is stated in the document that “pharmaceutically acceptable salts” are those intended to mean a salt that retains the biological effectiveness of the free acid and base form of the specified compound and that is pharmaceutically suitable. Examples of pharmaceutically acceptable salts at **Exhibit A and Exhibit A(1)** include maleates. The document further states that **in case of compounds, salts that are solids, it is understood by those skilled in the art that the compounds, salts and**

solvates may exists in different crystalline or polymorph forms [See Exhibit A columns 9 - 11].

- (iii) The salt forms of *rucaparib* have been claimed in the document at **Exhibit B**, WO2004/087713 A1, in which salts of 8-fluoro-2-(4-methylaminomethyl-phenyl)- 1, 3, 4, 5-tetrahydro-azepino [5, 4, 3- cd] indol- 6-one have been claimed. The document specifies the use of the compound for treatment of cancers and the amelioration of diseases. As cancer therapeutics, the compounds of the invention maybe used in combination with DNA damaging cytotoxic agents too. Though the document at **Exhibit B** does not specify the camsylate and maleate salt forms, it broadly claims the pharmaceutically acceptable salt form of the compound, and later specifically also claims the phosphate salt form [See **Exhibit B** page 3-6].
- (iv) The claims 1-25 in the present application are not novel, and have been prior claimed and published in the document at “**Exhibit C**”, US 2006 0074073 (Indian equivalent IN1514/DELNP/2007) that discloses and claims the dosage form of *Rucaparib* along with pharmaceutically acceptable salts, solvates and its combination with other anti-cancer agents. It specifically states that the compound is therapeutically effective for many types of cancers, including pancreatic cancer, ovarian cancer, etc. [See **Exhibit C** page 3 paras 0020-0027].

- (v) The document at **Exhibit C** also includes the camsylate and maleate salt forms of the said form of *rucaparib* [See **Exhibit C** pages 2- 4, paras 0009-0017, and 0043]. The structure of the compound at **Exhibit C** is exactly the same as that claimed in the present application, and envisages the salt forms too:-



- (vi) Thus, the present application is not novel, the compound and its salts forms have been known and envisaged in documents prior to the priority date of the application herein, and the impugned application ought to be rejected under Section 25(1)(b).

B. Section 25(1)(d): Prior public knowledge and prior use in India

- (i) The prior art documents at **Exhibits A to G**, the invention so far claimed in the present application for the salt forms of *rucaparib* and its use in the treatment as an anti-cancer agent has been known and used in India prior to the priority date of the impugned application.
- (ii) The pharmaceutically acceptable salt form of the compound and its use

thereof has been known. The camsylate and maleate salt forms have been known to have better stability, solubility, non-hygroscopicity and suitable for solid forms of the compound. The use of camsylate and maleate salts for *rucaparib* is not inventive, nor is it novel, it is in fact obvious and their use and properties as pharmaceutically acceptable salts have been known for decades. Thus the impugned application ought to be rejected on the ground of Section 25(1)(d) of the Patents Act.

C. Section 25(1)(e) : Obviousness and Lack of inventive step

- (i) The Opponent submits that the alleged invention clearly lacks an inventive step, and is obvious to a person of ordinary skills in the art. As such the Indian Patent Application 6460/CHENP/2012 is ineligible for grant of patent under section 25(1)(e) of the Patents Act.
- (ii) The Applicant states that the prior art used the phosphate salt form which was suitable for the intravenous dosage, but unsuitable for the solid dosage form. The applicant states that they have found the camsylate and maleate salt of *rucaparib* to be stable and not susceptible to hydration compared to other salt forms. However, these properties of the camsylate and maleate salt forms are known and use of them in solid dosage forms is not inventive.

- (iii) The Opponent submits that the document at “**Exhibit C**” discloses a list of salts used as the *rucaparib* salt forms, including the camsylate and maleate forms. **Exhibit A** also specifically discloses the maleate salt form of *rucaparib*.
- (iv) The pharmaceutical salts have been known since decades, and there is no novelty, no inventive step, and the uses of the salt forms are obvious to a person skilled in the art. Berge et al., 1977, the document annexed at “**Exhibit D**” discloses a list of 53 FDA approved commercially marketed salts used in pharmaceutical products which includes the camsylate and maleate salts. The document displays the knowledge that salt forms display physical, chemical, and thermodynamic properties to the parent compound – crystalline and hydrophobicity that affect the dissolution rate, stability, absorption, toxicity, hygroscopicity, etc. that affect bioavailability and solubility. The salt forms alter the physical, chemical, and biological characteristics of a drug without modifying the chemical structure. The Applicant of the impugned application would have been motivated to use the salts listed by the FDA and based on routine experimentation, identified the salts that would be suitably stable for *rucaparib* [See **Exhibit D** page 2, table 1].
- (v) The Applicant has made claims in the present application on the salt forms by specifying X-ray diffraction patterns, NMR spectrum, etc. It

may be noted that drug substances, salts, polymorphs, crystalline salt forms need to be thermodynamically stable or metastable form. Good knowledge of polymorphism and polymorphic stability is needed to predict long term stability of dosage forms, including crystalline and anhydrous crystalline forms. There are various techniques to study or investigate the solid state. These include x-ray, x-ray powder diffraction, thermal analysis, etc. Powder x-ray diffraction is both rapid and relatively simpler and is a known method of choice. It is unique to each polymorphic form, and are known in chemistry [See text book Herbert Lieberman, Leon Lachman and Joseph Schwartz, "Pharmaceutical Dosage Forms: Tablets" Volume 1, 1989; pages 38 – 41]. No patent can be claimed on techniques used to study the solid state of drug substances.

- (vi) Further, the Nuclear Magnetic Resonance (NMR) Spectroscopy are observational techniques used in chemistry to observe the behaviour of atomic nuclei when subjected to external magnetic field. NMR spectroscopy is particularly useful in the context of assessing the extent of ultraviolet and infrared spectra of heteroaromatic systems are in accord with their aromatic character, their properties, in determining the position of tautomeric equilibria and in testing for existence of non-insoluble intermediaries. These are known in heterocycle chemistry and no patent can be claimed on such techniques used in pharmaceutical

science. Thus, claims 3 - 10 and 13- 21 cannot be claimed nor granted in the present application, and the present patent application should be dismissed *in limine*.

- (vii) The camsylate salt used in pharmaceutical drugs has been known to be stable and its method of preparing has been known. The camsylate salt is known to form different crystal forms that have been well analysed via X-ray diffraction and NMR spectrum analysis. This has been revealed in the document annexed at **"Exhibit E"**, US 6936625 B2 titled "Amlodipine camsylate and method of preparing thereof". Camsylate salt forms have been used for treating various diseases, including cardiovascular diseases. Thus, there is no inventive step, and the properties of camsylate salts make it an obvious and preferred candidate for use as pharmaceutical salts for better stability, etc. [See **Exhibit E** columns 1, 2, 7 and table 4].
- (viii) The Opponent also submits that camsylate and maleate salts have been used in pharmaceutical science for decades for their known stability, better physicochemical properties and hygroscopicity. The document at **"Exhibit F"**, US 4489011 A, relates to certain oral "hypoglycaemic N-(2-substituted-3-dialkylamino - 2- propenylidene) - N- alkylalk-anaminium camsylate salts". The camsylate salts have better physiochemical properties. The document at **Exhibit F** shows that

camsylate salts have desirable solubility, high stability, non-hygroscopicity, and superior palatability when compared with other corresponding alkanaminium cations [See **Exhibit F** end of Column 1].

- (ix) Camsylate salts have been found to be better than conventional salts and are neither hygroscopic nor explosive, rendering them suitable for the preparation of conventional solid dosage forms with acceptably long shelf life. It also is physiologically inert and thus introduces no unwanted side effects during long term administration [See **Exhibit F** Column 2].
- (x) The document at **Exhibit F** displays the better properties of camsylate salt and makes it the obvious choice of a person with ordinary skills in the art.
- (xi) Similarly, maleate salts also have been known for their properties to be the obvious choice for use in pharmaceutical drugs. The document at "**Exhibit G**" is US 4879303 "Pharmaceutically acceptable salts". Though the document is for the besylate salt form, it describes the properties of stability, etc. of the maleate salt form too. It can be seen in Table 1 of the document at **Exhibit G**, that the maleate salt has good solubility, like the besylate salt, and is pretty stable too. The document also describes that "only maleate, tosylate and besylate salts do not pick

up any moisture when exposed to 75% relative humidity at 37 degrees Celsius for 24 hours [See **Exhibit G** Column 2, Table 1 and Column 3].

(xii) The document at **Exhibit G** states that in order to be suitable for this purpose, the pharmaceutically acceptable salt must satisfy the following four physiochemical criteria: i. good solubility; ii. Good stability; iii. Non-hydroscopicity; and iv. Processability for tablet formulations, etc. [See **Exhibit G** Column 2].

(xiii) Thus, the document at **Exhibit G** makes maleate salt also the obvious choice for *rucaparib*.

(xiv) For all the above reasons, the present patent application ought to be dismissed, as there is no novelty, no inventive step and is obvious to a person with ordinary skills in the art.

D. Section 25(1)(f): Not an invention within the meaning of the Patents Act.

(i) It has been shown by the prior art documents annexed in the present Pre-grant Opposition that the complete specification and the amended claims do not constitute an invention. The alleged invention so far claimed is neither a new product nor a new process nor does it involve an inventive step as there is no technical advance as compared to existing knowledge

and the alleged invention is obvious to a person skilled in the art. In fact, the alleged invention is a salt form of a known substance or compound and cannot be patented in India.

(ii) The claims of the present Application also do not meet the test prescribed under Sections 2(1)(j) and 2(1)(ja) of the Act and hence the application ought to be dismissed *in limine*.

(iii) The Opponent strongly submits that the alleged invention falls within the ambit of **Section 3(d)** and hence is not patentable. The definition of Section 3(d) read alongwith explanation is relevant and validly applicable for the alleged subject matter:

Sec. 3(d) of the Act reads as “*the mere discovery of a new form of a known substance* which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the *mere use of a known process*, machine or apparatus unless such known process results in a new product or employs at least one new reactant” is **not patentable** under the Act.

*Explanation:- For the purpose of this clause, **salts**, esters, ethers, **polymorphs, metabolites**, pure form, particle size, isomers mixtures of isomers, complexes, combinations and other derivatives **of known***

substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.”

- (iv) It is an established position of the law that if a discovery is made from a known compounds, a duty is cast upon the patent applicant to show that the discovery had resulted in the enhancement of a known efficacy of that substance [See *Novartis AG v. Union of India and others*, (2007), 4 MLJ 1153, page 15]. The Hon’ble Intellectual Property Appellate Board has also held in *Novartis AG v. Union of India and Others*, IPAB, 26.06.2009, at pages 178 and 179, that “efficacy” in Sec. 3(d) means therapeutic efficacy.
- (v) Salts, polymorphs, etc. of known substances are considered to be the same substance and are not patentable under Section 3(d) of the Patents Act. The impugned application is for the salt forms of *rucaparib* and is hit by Section 3(d) of the Patents Act, and the impugned application should be rejected *in toto*.
- (vi) The impugned application does not speak of the efficacy of *rucaparib*’s salt forms or enhanced properties, if any. The application only focuses on improvement of certain physiochemical parameters by using the maleate and camsylate salt forms for their hygroscopic properties in a solid form over the prior art of the phosphate salt of *rucaparib*.

However, as seen in the prior art annexed to this Opposition, it is clear that the properties of maleate and camsylate salt forms have been known and their use in *rucaparib* is not patentable as it is a mere discovery of a new form of a known substance, namely, salt and polymorph forms of *rucaparib*, with known properties and processes and no new reactants, making it to be the one and the same substance, that is, *rucaparib*.

- (vii) Further, some of the claims in the present application for techniques to analyse the solid forms of drug substances are not only frivolous but are known scientific principles and are hit by Section 3(a) and 3(c) of the Patents Act and cannot be patented.
- (viii) The prior art documents at **Exhibit A to G** not only describe the broad acceptable pharmaceutical salt forms of *rucaparib* but also describe the maleate and camsylate salt forms and show clearly why they would be the obvious choice for the pharmaceutical product.
- (ix) The claims in the impugned application at claim 23 and 24 for the method of treating the disease condition and method of treating cancer fall within the meaning of inventions not patentable under Section 3(i). Hence, not patentable.
- (x) In view of the above, the claims from claim 1 to 22 and 25 of the

impugned application ought to be rejected under section 25(1)(f) read with section 3(d) of the Patents Act, being the salt form of a known substance lacking enhanced therapeutic efficacy. Claims 23 and 24 of the impugned application ought to be rejected under section 25(1)(f) read with section 3(i) of the Patents Act, being methods of treatment, administration of the pharmaceutical composition of salts of *rucaparib* which are not patentable. Thus the impugned application ought to be rejected *in toto*.

37. It is submitted by the Opponent that all the above-mentioned prior art documents annexed to the present Pre-grant Opposition destroy the novelty of the alleged invention so claimed by the Applicant. The information in the prior art documents disclose the essential elements of the alleged invention. Novelty is destroyed when the essential elements have been disclosed, even if the details of executing the invention, or clear description of its properties or method of making it were not disclosed.
38. In *Enercon (India) Limited v. Aloys Wobben* ORA/6/2009/PT/CH, ORDER (No. 18 of 2013) the Intellectual Property Appellate Board of India noted that novelty may be denied on the basis of 'inherent anticipation'. It stated: "*the prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating prior art..... it is not necessary that inherent*

anticipation requires that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. But it is necessary that the result is a necessary consequence of what was deliberately intended in the invention."

Thus, the novelty in the present application is destroyed by all prior art documents cited herein.

39. It is further submitted that the inventive step claims in the present application are destroyed as what is claimed is obvious to a person skilled in the art, i.e. there is reasonable expectation of success embedded in the prior art which motivates a skilled person to arrive at the alleged claimed invention. Obviousness cannot be avoided by showing some degree of unpredictability in the art, so long as there was a reasonable probability of success through disclosures provided in the prior art documents. Obviousness does not require absolute predictability of success. All that is required is reasonable expectation of success in the matter of pharmaceutical inventions. All the prior art documents annexed to this Opposition provide a reasonable predictability of success and the claimed compound is obvious to a person skilled in the art. Additionally, the claimed compounds do not involve a technical advance compared to existing knowledge.
40. The Opponent states that grant of patents to the Applicant in other jurisdictions cannot tantamount to a grant of a patent in India. The Indian law is different from the laws in other jurisdictions and care has been taken by the law makers

not to allow patents for pharmaceutical products that are not genuinely inventive or that are known earlier, or obvious to a person skilled in the art. The law specifically prohibits grant of patents for salts, polymorphs, etc. of known substances and also prevents abuse of the patent process by laying down grounds for opposition that prevent undeserving patents from being granted.

41. The Opponent states that the present Application No. 6460/CHENP/2012 falls within the category of non-patentable inventions as described in Section 3(d) and 3(i) of the Patents act, and also does not meet the definition of “invention” and inventive step as set out in Section 2(1)(j) and 2(1)(ja) of the Act. The present Application ought to be rejected *in toto* under Section 25(1) read with clauses (j) and (ja) of section 2(1) and clause (d) of Section 3 of the Act.

42. **Prayers**

Having established non-patentability of the alleged invention and having adduced supporting evidence for each of the above grounds of Opposition, Opponent prays for the following reliefs:

- a. That the Applicant’s Patent Application No. 6460/CHENP/2012 having filed, with original claims as well as amended claims, be rejected *in toto* and the grant of Patent to the Applicant be refused.
- b. That the Opponent be granted leave to file further arguments and evidence against the impugned application.
- c. That copy of the reply of the Applicants and evidence, if any, be forwarded to the Opponent along with amendment to claims, if any;

- d. That the Opponent be granted leave to file response/rejoinder to the reply and the evidence of the Applicants.
- e. That the Opponent should be given an opportunity to oppose the amended claims, if any.
- f. That the Opponent be granted hearing in this case.
- g. That the Opponent be granted leave to refer to and rely upon full text of the documents referred to in this opposition.
- h. Such other and further relief/s be granted to the Opponent, as the Ld. Controller may deem fit in the facts and circumstances of this case.
- i. That the Opponent be awarded costs.

All communications relating to these proceedings may be sent to the following address in India:-

Dr. GOPAKUMAR G. NAIR
Gopakumar Nair Associates
3rd floor, Shivmangal, Next to Big Bazaar
Akurli Road, Kandivli (East), Mumbai-400101
Maharashtra, India. Phone: 91-22-40895454
E-mail address: gopanair@gnaipr.net

Dated this 10th day of October, 2017



Dr. GOPAKUMAR G. NAIR
Regn. No: IN/PA 509
(Agent for the Opponent)
Gopakumar Nair Associates

To,
The Controller of Patents
The Patent Office, Chennai